CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209500
PDUFA Goal Date	December 27, 2019
OSE RCM #	2018-2110
Reviewer Name(s)	Sangeeta Tandon, PharmD, MPH
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 19, 2019
Subject	Evaluation of Need for a REMS
Established Name	lumateperone tosylate
Trade Name	Caplyta
Name of Applicant	Intra-Cellular Therapies, Inc.
Therapeutic Class	Atypical Antipsychotic
Formulation(s)	42mg capsules
Dosing Regimen	42 mg by mouth once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Caplyta (lumateperone), is necessary to ensure the benefits outweigh its risks. Intra-Cellular Therapies, Inc. (Applicant) submitted a New Drug Application (NDA) 209500 for lumateperone with the proposed indication for the treatment of schizophrenia in adults. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM determined that a REMS is not needed to ensure the benefits of lumateperone outweigh its risks. This decision is supported by the review of the safety data in the clinical and nonclinical development program. Potential safety concerns were identified for lumateperone in nonclinical studies that included dogs and rats. The neuro-pathological findings and signs of neurotoxicity observed in dogs after long-term exposure to lumateperone, as well as cardiomyopathy, retinal degeneration and peripheral neuropathy observed in the mouse and rat studies raised concerns about whether similar toxicities might occur in humans after long-term exposure. The review team concluded if there was a reasonable possibility of human safety risks, the overall benefit/risk determination would not support approval of lumateperone. However, during the review of the NDA, further nonclinical and clinical studies conducted by the Applicant provided additional data that these toxicities do not appear to be relevant to human use because the metabolic pathway for humans (glucuronidation) differs from that seen in animal species. Review of adverse events, concomitant medication starts, and physical examination findings during 1-year of lumateperone exposure did not reveal any signals suggesting that humans experienced safety findings consistent with those seen in animal studies. The nonclinical safety findings in dogs, rats, and mice will be described in Section 13.2 of the proposed Prescribing Information (PI), along with discussion of review conclusions related to these toxicities. The Agency is requiring a postmarketing commitment (PMC 3760-6) to further characterize the drug interaction potential of lumateperone and its major metabolites with drug transporters and enzymes to further explore this theoretical concern. Lastly, the treatment-emergent adverse events that occurred in the clinical development are in general consistent with other approved atypical antipsychotics. Thus, at this time, there is no identified safety concern that warrants a REMS to ensure the benefits of lumateperone outweigh the risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME),[a] Caplyta (lumateperone), is necessary to ensure the benefits outweigh its risks. Intra-Cellular Therapies, Inc. (Applicant) submitted a New Drug Application (NDA) 209500 for lumateperone with the proposed indication for the treatment of schizophrenia in

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

adults. This application is under review in the Division of Psychiatry (DP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Lumateperone is proposed for the treatment of schizophrenia in adults. It is a serotonin $5HT_{2A}$ receptor antagonist, a dopamine receptor phosphoprotein modulator (DPPM), and a serotonin transporter (SERT) inhibitor. The overall binding profile for lumateperone is consistent with other marketed atypical antipsychotic agents except for a relatively high affinity binding to the SERT, although the functional consequence of this was not assessed by the Applicant. Most other antipsychotics do not bind to the SERT.

The mechanism of action in the treatment of schizophrenia is unknown. However, like other antipsychotics, the efficacy could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} and dopamine D_2 receptors. The proposed dose of lumateperone is 42 mg by mouth once daily intended for chronic oral administration[b] and dose titration is not required.

Lumateperone is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for lumateperone NDA 209500 relevant to this review:

- 06/05/2018: The first half of the NDA 209500 submission for the treatment of schizophrenia was received
- 09/27/2018: The second half of the NDA 209500 submission for the treatment of schizophrenia received
- 12/10/2018: The Agency filed the NDA 209500
- 04/09/2019: Mid-cycle Communication to include major safety concern/risk management: further evaluation of nonclinical findings in the rat and mouse by a veterinary neuropathologist is required and evaluation of how best to incorporate nonclinical data on neurotoxicity from the carcinogenicity studies into the estimation of neurotoxicity risk for humans
- 07/18/2019: Late Cycle Meeting held via teleconference; discussed difficulty for Agency to reach a conclusion on the long-term safety of lumateperone for humans based on several elements of the available nonclinical data. Additional nonclinical studies and additional analyses of existing nonclinical samples are required in order to clarify the

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

mechanisms of toxicities observed in the animal studies and establish that these toxicities were unlikely to occur in humans.

- 07/25/2019: Major Amendment letter received to extend initial NDA review, documenting a plan for additional nonclinical studies and data analyses.
- 07/31/2019: Major amendment acknowledgment letter sent to the Applicant; PDUFA goal date extended to December 27, 2019.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) outlines certain criterion to make a diagnosis of schizophrenia, a serious mental illness which is thought to affect approximately 20 million people worldwide.[1] Schizophrenia involves a range of cognitive, behavioral, and emotional symptoms, and is characterized by positive and negative symptoms that may include delusions, hallucinations, disorganized speech, disorganized behavior, diminished emotional expression, apathy, avolition, decreased reasoning and social cognition, as well as other mood and anxiety symptoms.[2,3] There is no physical or lab test specific for schizophrenia, and diagnosis involves the recognition of a criterion of symptoms negatively impacting social or occupational functioning. Estimates of the prevalence of schizophrenia and related psychotic disorders in the U.S. range between 0.25% and 0.64%.[1] Schizophrenia is one of the top 15 leading causes of disability worldwide and individuals with schizophrenia have an increased risk of premature mortality.[1,c]

4 Description of Current Treatment Options

There are 23 antipsychotics approved in the United States for the treatment of schizophrenia. Antipsychotics are generally classified as first-generation (typical) antipsychotics and second-generation (atypical) antipsychotics based on their affinity for dopamine and/or serotonin receptors and associated adverse events. The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D_2 receptors and/or serotonin 5-HT_{2A} receptors. In general, typical antipsychotics have a higher risk for causing extrapyramidal side effects (EPS), such as dystonia, parkinsonism, and tardive dyskinesia, and many atypical antipsychotics are associated with significant weight gain and metabolic effects.[4]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

Table 1 below provides the FDA-approved therapies for the treatment of schizophrenia.

Table 1: FDA-approved Antipsychotics for the Treatment of Schizophrenia

First-Generation Therapies	Second-Generation Therapies
Chlorpromazine	Asenapine
Fluphenazine	Clozapine
Mesoridazine	Cariprazine
Haloperidol	Iloperidone
Perphenazine	Lurasidone
Thioridazine	Olanzapine
Molindone	Paliperidone
Thiothixene	Quetiapine
Trifluperazine	Risperidone
Loxapine	Ziprasidone
Prochlorperazine	Brexpiprazole
	Aripiprazole

Of the 23 medicines provided on Table 1, Clozaril (clozapine), Zyprexa Relprevv (olanzapine) and Adasuve (loxapine) are the only antipsychotics approved with a REMS. The risk identified for clozapine (severe neutropenia) is unique to clozapine; the risk for Zyprexa Relprevv (negative outcomes associated with Zyprexa Relprevv post-injection delirium/sedation syndrome) is unique to the formulation, a long-acting intramuscular injection which may result in unintentional rapid increase in serum olanzapine concentrations in some patients; the risk for Adasuve (negative outcomes (respiratory distress or respiratory arrest) associated with Adasuve induced bronchospasm) is unique to the formulation; these risks do not extend across the antipsychotic class.

In addition to antipsychotic medications, patients with schizophrenia are often treated with adjunctive medications to treat co-morbidities and the EPS-related adverse events associated with antipsychotics. These adjunctive medications include anticholinergics, beta-blockers, benzodiazepines, and antidepressants.

Psychosocial treatments are recommended for use alongside antipsychotic therapy that may reduce relapse risk, improve coping skills, improve social/vocational functioning, and help individuals with schizophrenia function more independently. These psychosocial interventions include cognitive behavioral therapy, social skills therapy, assertive community treatment, and supported employment. Individual patients often require trials of numerous antipsychotics before an optimal treatment is identified and there are some patients for whom an effective

treatment cannot be identified despite multiple trials. Thus, having additional treatment options in the armamentarium is valuable.

5 Benefit Assessment

The clinical studies supporting the proposed indication of the treatment of schizophrenia are Studies 005 (4-week; n=335) and 301 (4-week; n=450) which met their primacy efficacy endpoint with lumateperone 42 mg dose, where study 302 (6-week; n=696) did not provide evidence that lumateperone was superior to placebo for the treatment of schizophrenia. [3,4,5] All studies were multi-center, randomized, double-blind, and placebo-controlled, conducted in the US, and the primary efficacy endpoint was the change from baseline to end of treatment (Day 28 for Studies 005 and 301; Day 42 for Study 302) on the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a clinician-rated measure that includes items assessing the severity of positive symptoms, negative symptoms, and general psychiatric symptoms associated with schizophrenia. The change from baseline to end of treatment on the Clinical Global Impression – Severity (CGI-S) measure was a secondary endpoint in Study 005 and a key secondary endpoint in Studies 301 and 302. The CGI-S scale is a 7-point scale for rating symptom severity in patients with psychiatric disorders. The clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis. The studies allowed, if necessary, concomitant administration of lorazepam to help alleviate agitation or insomnia, benztropine for treatment of extrapyramidal adverse effects, and propranolol for treatment of akathisia.

Study 005 inclusion criteria consisted of 18-55 year old male or female patients. Of the 335 patients randomized, 84 patients were in the lumateperone 42 mg, 84 in lumateperone 84 mg, 82 in risperidone 4 mg, and 85 patients in the placebo treatment arms. One randomized patient in the 84 mg group was discontinued from the study at the patient's request prior to receiving study drug.

Studies 301 & 302 enrolled 18-60 year old male or female patients. In Study 301, of the 450 patients randomized, 150 patients were assigned to the three treatment groups: lumateperone 42 mg, lumateperone 28 mg and to placebo. One randomized patient in the 84 mg group was discontinued from the study at the patient's request prior to receiving study drug. In study 302, of the 696 patients randomized, 174 patients were assigned to the four treatment groups: lumateperone 42 mg, lumateperone 16 mg, risperidone 4 mg daily and to placebo.

The clinical reviewer concluded that both Studies 005 and 301 demonstrated efficacy for the 42-

mg dose only.[d] Of note, the results from Study 302 did not provide evidence that lumateperone was superior to placebo for the treatment of schizophrenia, however, these findings did not change the conclusion of effectiveness for the 42 mg dose as demonstrated by Studies 005 and 301.[5] Because efficacy has not been demonstrated for the 14 mg, 28 mg, or 84 mg doses of lumateperone, the product label will include only lumateperone 42 mg as an approved dose of the drug.

6 Risk Assessment & Safe-Use Conditions

The safety data from the 3 controlled studies were supplemented by data from an open-label, long-term, uncontrolled study (Study 303; n=603) of lumateperone in patients with schizophrenia. Thus, the safety population included a total of 1949 patients exposed to at least one dose of lumateperone, which were analyzed according to the actual treatment received.

There were 3 deaths in clinical development program; two of the deaths (Studies 301 & 302) did not involve patients in the lumateperone treatment arms and the remaining death (Study 303) occurred two weeks after the last dose of study drug and is unlikely to have been related to lumateperone administration.

The potential safety concern for lumateperone was based on findings from nonclinical studies in dogs and rats. There was concern about the neuropathological findings and signs of neurotoxicity observed in dogs after long-term exposure to lumateperone, as well as cardiomyopathy, retinal degeneration and peripheral neuropathy observed in the mouse and rat studies, which raised concerns about whether similar toxicities might occur in humans after long-term exposure. However, data suggest that the nonclinical findings are not relevant to humans. In the clinical development program, humans receiving lumateperone 42 mg for up to 12 months (Study 303) did not exhibit safety findings suggestive of those seen in dogs and rats. Review of adverse events, concomitant medication starts, and physical examination findings during 1-year of lumateperone exposure did not reveal any signals suggesting that humans experienced safety findings consistent with those seen in animal studies (i.e., cardiomyopathy, neuropathy, or retinal degeneration). During the course of the review, further nonclinical and clinical studies conducted by the Applicant provided additional data which supports that these toxicities were attributed to exposure to aniline metabolites, and subsequent accumulation of pigmented material in lysosomes, that are developed in dogs and rats through their enzyme pathway that is different from the pathways used by humans (glucuronidation). T. Additional clinical studies enrolling patients with at least six months of exposure to lumateperone 42 mg daily demonstrated that the aniline metabolites could not be detected in human circulation at the level of quantification at

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

which the aniline metabolites were detected in the dog. Although the Agency cannot completely rule out the presence of very low levels of aniline metabolites in humans treated with lumateperone (i.e., levels that are below the level of detection of available bioanalytical methods), the lack of detectable quantifiable levels of aniline metabolites in humans treated with lumateperone, the plausible metabolic rationale by which anilines would accumulate in animal species but not in humans, and the absence of evidence from in the long-term human studies of the pattern of aniline-related toxicities that occurred in the animal studies provide support that the nonclinical safety findings do not appear to be relevant to humans. Therefore, the nonclinical safety findings in dogs, rats, and mice will be described in Section 13.2 of the proposed Prescribing Information (PI), along with discussion of review conclusions related to these toxicities.[6] The Agency is requiring a postmarketing commitment (PMC 3760-6) to further characterize the drug interaction potential of lumateperone and its major metabolites with drug transporters and enzymes to further explore this theoretical concern.

Regarding the treatment-emergent adverse events, these are in general consistent with other approved atypical antipsychotics[7,8, 9,10] The most common adverse reactions to lumateperone were somnolence/sedation, nausea, dry mouth, dizziness, creatine phosphokinase increased and elevated liver enzymes.[e] Similar to other antipsychotics, lumateperone contains a boxed warning, based on safety concerns from the antipsychotic drug class, of increased mortality in elderly patients with dementia-related psychosis. Section 5 *Warnings and Precautions* in the PI for lumateperone include safety concerns also based on the drug class; these include cerebrovascular adverse reactions in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia, metabolic changes (hyperglycemia and hyperlipidemia), leukopenia, neutropenia, and agranulocytosis; orthostatic hypotension and syncope, falls, seizures, cognitive and motor impairment, body temperature dysregulation, and dysphagia. High-exposure to lumateperone may increase the risk of QTc prolongation, therefore the PI will include information in section 2.2 to avoid concomitant administration with moderate and strong CYP3A4 inhibitors and is not recommended in patients with hepatic impairment.

The known risks of lumateperone will be managed through product labeling, postmarketing studies, and ongoing post-marketing pharmacovigilance will be important to monitor for safety signals that were not observed in the development program. Appendix A provides a summary of the postmarketing requirements and commitments.

7 Expected Postmarket Use

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Lumateperone will likely be used by psychiatrists and primary care providers to manage patients with schizophrenia in any treatment setting, inpatient or outpatient. Since schizophrenia is a lifelong condition, lumateperone will most likely be used as a chronic outpatient medication, with or without other concomitant treatments for schizophrenia. Since schizophrenia often requires multidisciplinary efforts/therapies, if approved, it may be use broadly in the patient population diagnosed with schizophrenia.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lumateperone beyond routine pharmacovigilance and labeling.

9 Discussion of Need for a REMS

Lumateperone is a serotonin $5HT_{2A}$ receptor antagonist, dopamine receptor phosphoprotein modulator, and a SERT inhibitor that is proposed for the treatment of schizophrenia in adults.

Currently, there are over 23 antipsychotics approved for the treatment of schizophrenia in the US. Most of these medicines are approved without a REMS, with the exception of Clozaril, Zyprexa Relprevv, and Adasuve, for which the risks are unique to those specific products and do not extend across the antipsychotic class.

Lumateperone efficacy and safety in the treatment of schizophrenia in adults is supported by 4 clinical studies; 2 of the studies support efficacy of the 42 mg dose of lumateperone only and all provide safety data. The clinical reviewer recommends approval of lumateperone for schizophrenia based on the efficacy and safety information currently available. The treatment emergent adverse events that occurred with lumateperone are consistent with those seen for the antipsychotic class and can be managed with labeling and routine pharmacovigilance.

The review team considered whether a REMS should be required for evaluating and mitigating the theoretical human risks related to the nonclinical toxicology findings. The team concluded that if there was a reasonable possibility of human safety risks related to aniline metabolites, the overall benefit/risk determination would not support approval of lumateperone. However, during the review, the Applicant provided additional data supporting the clinical reviewer's position that the nonclinical findings do not appear to be relevant to human use. The nonclinical safety findings in dogs, rats, and mice will be described in Section 13.2 of the PI, along with discussion of review conclusions related to these toxicities. Furthermore, the Agency will require a PMC (#3760-6) to further evaluate this theoretical risk. Thus, there is no remaining safety issue that warrants consideration of a REMS at this time.

Therefore, we agree with the clinical reviewer that the risks associated with lumateperone use at recommended dose in schizophrenia are expected to be manageable in the context of standard

clinical care and that measures beyond labeling are not necessary for the benefits of lumateperone to outweigh the risks.

10 Conclusion & Recommendations

DRM determined that a REMS is not necessary to ensure the benefits of lumateperone outweigh the risk. This decision is supported by the clinical review of the safety data in the development program and additional data provided by the Applicant during review of the NDA. All known safety concerns will be addressed in the Warnings and Precautions and other sections of the PI, which will inform healthcare providers about the risks and subsequent recommendations for management. Theoretical clinical implications of safety findings from the nonclinical studies in dogs and rats will be further evaluated in a postmarketing commitment.

Should Division of Psychiatry have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

11 Appendices

11.1 Appendix A. Postmarketing Requirements and Commitments

The following post-marketing requirements will be requested in accordance with PREA. Please refer to Section 10 (Pediatrics) for additional discussion.

- PMR #3760-1: Conduct an open-label , multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics of lumateperone in patients ages 13 to 17 years diagnosed with schizophrenia.
    - Purpose: to characterize the pharmacokinetics of lumateperone and its metabolites and assess the safety of lumateperone in adolescents.
    - Acceptable to assess post-approval following establishment of safety and efficacy in adults.
- PMR #3760-2: Conduct a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lumateperone for the treatment of schizophrenia in patients aged 13 to 17 years.
    - Purpose: to determine whether lumateperone is effective and safe for treatment of schizophrenia in adolescents.
    - Acceptable to assess post-approval following establishment of safety and efficacy in adults.

- PMR #3760-3: Conduct an open-label study to assess the long-term safety of lumateperone in patients aged 13 to 17 years diagnosed with schizophrenia.
    - Purpose: to assess the long-term safety of lumateperone for the treatment of schizophrenia in adolescents.
    - Acceptable to assess post-approval following establishment of safety and efficacy in adults.

The following post-marketing requirement will be requested in accordance with FDAAA:

- PMR #3760-4: Perform a lactation study (milk only) in lactating women who have received therapeutic doses of lumateperone using a validated assay to assess concentrations of lumateperone in breast milk and the effects on the breastfed infant.
    - Purpose: to provide data on the presence of lumateperone in human milk and the effects on the breastfed infant.
    - Acceptable to assess post-marketing because only a small subpopulation (lactating females) is affected and it is only feasible to conduct the study post-approval.

The following post-marketing requirement will be requested to further characterize the PK of lumateperone and assess for potential clinical implications if UGT inhibitors are used concomitantly with CAPLYTA:

- PMR #3760-5: Conduct a clinical pharmacokinetic trial to evaluate if UGT enzyme inhibitors alter the PK of lumateperone and its metabolites (including metabolites IC201337 and IC201338) using fully validated assays and to determine appropriate dosing recommendations for CAPLYTA with regard to use of concomitant UGT enzyme inhibitors.
    - Purpose: to evaluate whether dosage adjustment for CAPYLYTA is necessary when it is used concomitantly with UGT enzyme inhibitors.
    - Acceptable to assess post-marketing because the overall benefit/risk profile of the drug appears favorable; there are uncertainties about aspects of the drug's safety profile in the specific subpopulation of patients who are prescribed co-medications that are UGT inhibitors.

The following post-marketing commitment will be requested to further characterize the drug interaction potential of lumateperone and its major metabolites with drug transporters and enzymes:

- PMC #3760-6: Conduct standard in vitro assays to determine:

- Substrate potential of lumateperone for OATP1B1/1B3;
- Inhibitor potential of lumateperone towards P-gp and BCRP;
- Inhibitor potential of all major metabolites (IC200131, IC200161, IC200565, IC201308, IC201309, and IC200056-enol-glu), if not yet evaluated, towards:
  - transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, and MATE2K;
  - inhibitor/inducer potential towards major CYP450 isoenzymes, except CYP3A (in vivo study with midazolam has been conducted).

- Purpose: to further characterize the drug interaction potential of lumateperone and its major metabolites with drug transporters and enzymes.
- Acceptable to assess post-marketing because the study is to further explore a theoretical concern that does not impact the approval determination.

The following post-marketing commitment will be requested for further efficacy evaluation:

- PMC #3760-7: Conduct a placebo-controlled randomized withdrawal maintenance study of lumateperone in patients with schizophrenia.
  - Purpose: to investigate the maintenance of efficacy over time for patients with schizophrenia who have been stabilized on lumateperone.
  - Acceptable to assess post-marketing because the benefit/risk profile of the drug appears favorable, but uncertainties about the long-term efficacy remain.

The following post-marketing commitment will be requested to develop appropriate lower strengths of CAPLYTA to allow for dosage adjustment in certain clinical scenarios:

- PMC #3760-8: Develop new strengths of 10.5 mg and 21 mg of CAPLYTA to meet the need for dose adjustment in patients with moderate to severe hepatic impairment and in patients who are taking concomitant strong or moderate CYP3A inhibitors.
  - Purpose: to develop appropriate new strengths for dosage adjustment when certain intrinsic/extrinsic factors are present that will impact lumateperone exposure.
  - Acceptable to develop post-approval because only small subpopulations are affected (e.g., patients with hepatic impairment or patients taking concomitant strong or moderate CYP3A inhibitors), and because initial labeling will state that use in those subpopulations should be avoided.

11.2 REFERENCES

[1] National Institute of Mental Health. Schizophrenia. Updated May 2018. https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml

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[10] Quetiapine. Prescribing Information (last updated August 2019).

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/s/

SANGEETA N TANDON
12/19/2019 01:03:51 PM

SELENA D READY
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